(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 September 2005 (29.09.2005)

PCT

(10) International Publication Number
WO 2005/090360 A1

(51) International Patent Classification[7]: C07D 501/22

(21) International Application Number:
PCT/IB2005/000652

(22) International Filing Date: 15 March 2005 (15.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
247/CHE/2004 19 March 2004 (19.03.2004) IN

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,

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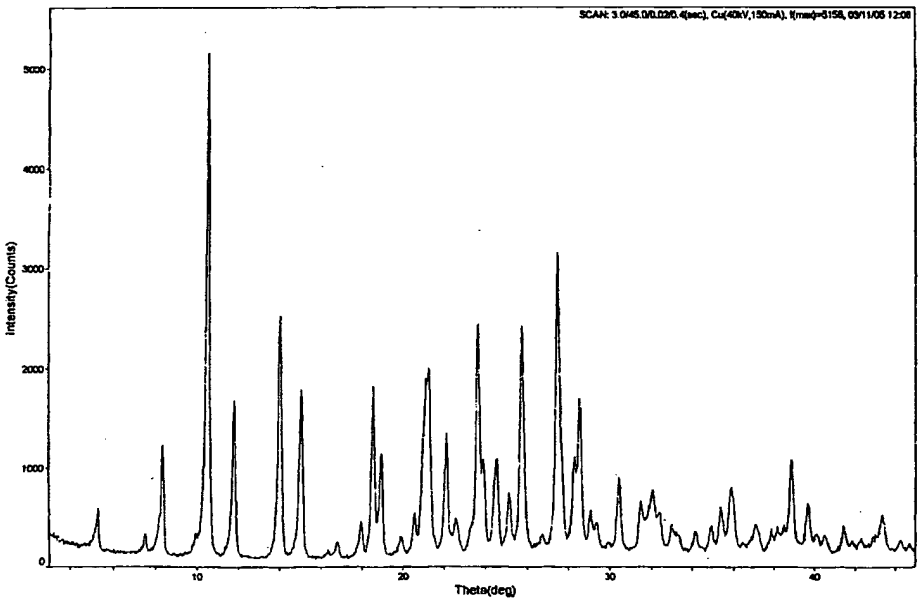
(54) Title: NOVEL POLYMORPH OF CEFDINIR



(57) Abstract: The present invention relates to novel polymorph of cefdinir represented by formula (I). More particularly, the present invention relates to novel crystalline form (Crystal D) of cefdinir. The present invention also provides a process for the preparation of novel crystalline form (Crystal D) of cefdinir.

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SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

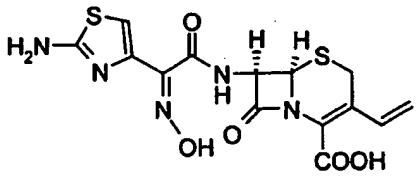
Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

NOVEL POLYMORPH OF CEFDINIR

Field of the Invention

The present invention relates to novel polymorph of cefdinir represented by formula (I). More particularly, the present invention relates to novel crystalline Form D of cefdinir.



(I)

The present invention also provides a process for preparing novel crystalline Form D of cefdinir.

Background of the Invention

Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum over the general gram positive and gram negative bacteria, especially against *Streptococci,* than other antibiotics for oral administration.

Cefdinir is a very useful anti microbial agent and was first time described in U.S. Pat.No.4,559,334. The US patent 4,935,507 disclosed that cefdinir reported in US Pat.No.4,559,334 is a crystalline like amorphous product, not a crystalline product and has disadvantages like it is bulky, not so pure, unstable and insufficient in filtration rate, therefore it is not suitable for a pharmaceutical product or is not easy to handle in the pharmaceutical preparations, in producing it in a large scale or in storage.

US patent number 4,935,507 claims the novel crystalline Form (Crystal A) of the cefdinir and a process for preparing the same. The X-ray crystallography data given in this patent is as given in the following table:

2θ°	I%
14.7	76
17.8	56
21.5	100
22.0	70
23.4	38
24.4	80
28.0	40

The crystalline Form (Crystal A) of cefdinir is disclosed in US 4,935,507 is prepared by dissolving 7-[2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid (*syn isomer*)(an amorphous product) as a salt with alkali metal in a solvent and adjusting the pH at room temperature.

US patent application publication no 2003/0204082 discloses a new crystalline Form which has high stability but a dissolution rate less than that of crystal-A.

In view of the vital antibiotic activities of cefdinir of the formula (I), the inventors of the present invention succeeded in obtaining the compound (I) in novel crystal Form, i.e. Crystal D, by adjusting the pH of a solution of cefdinir salt in mixture of water and organic solvent to 2.5 to 2.7 at low temperatures to get cefdinir with new crystal lattice which has better stability.

Objectives of the Invention

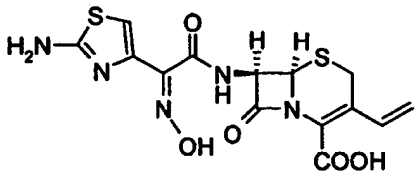
The main objective of the present invention is to provide novel crystalline Form D of cefdinir.

Another objective of the present invention is to provide novel crystalline Form D of cefdinir, which has better stability and useful for developing different dosage forms.

Another objective of the present invention is to provide process for novel crystalline Form D of cefdinir

Summary of the Invention

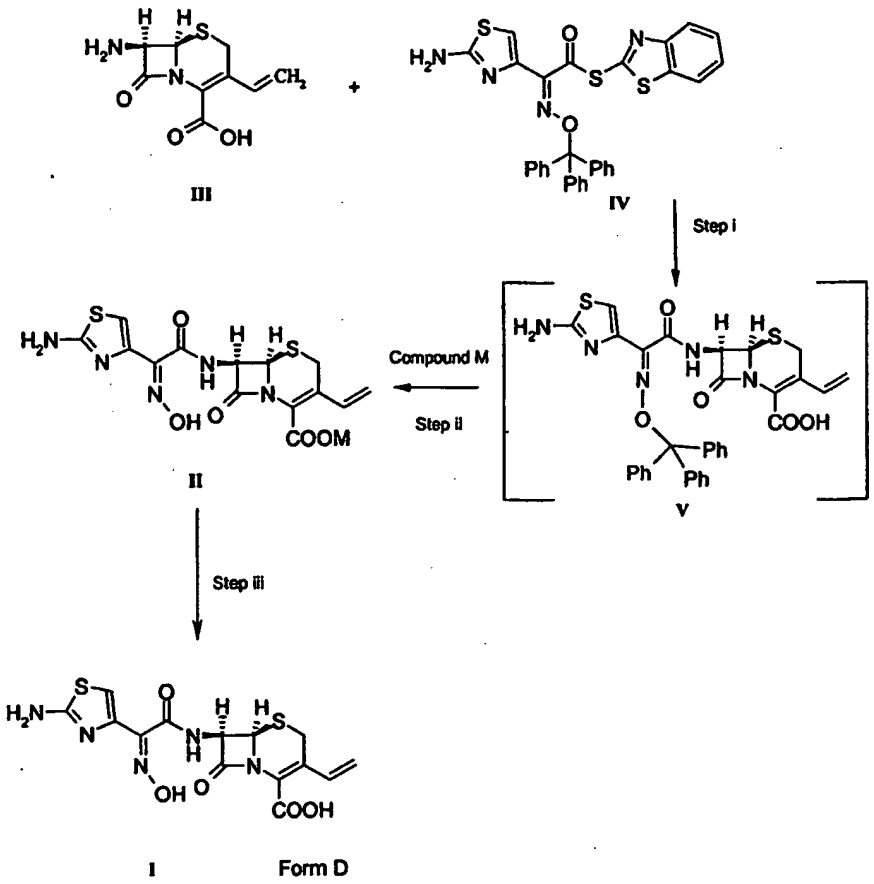
Accordingly, the present invention provides novel crystalline Form D of cefdinir of the formula (I)



(I)

having substantially the same X-ray diffractogram as set out in FIG. 1 and substantially the same IR spectrum, in a KBr, as set out in FIG. 2.

The present invention also provides a process for the preparation of novel crystalline Form D of cefdinir of the formula (I), which comprises the steps as per the scheme: 1



SCHEME 1

An embodiment of the present invention provides a process for the preparation of compound of formula (II), which comprising the steps of:

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (III) with compound of the formula (IV) in the presence of a base and solvent to give trityl intermediate of formula (V)

ii) hydrolyzing the trityl intermediate of formula (V) insitu with an acid in the temperature range of 35-75° C to give freebase, which is treated with compound M to produce a compound of formula (II) where in compound M is group which forms salt with Cefdinir in mixture of organic solvent and water

iii) converting the compound of formula (II) into Cefdinir Form D.

In another embodiment of the present invention, provides a process for the preparation of Form D from the compound of formula (II), which comprising the steps of:

a) dissolving the compound of formula (II) in mixture of solvents, acidifying the solution to pH 0.5 – 2.0 preferably at 1.3 to 1.5 at a temperature in the range of 10 to 50 °C and preferably at 15 to 36°C

b) adjusting the pH of solution obtained from step (a) to 4.0 - 6.5 using a base and treating with charcoal at a temperature in the range of 10-50 °C preferably at 15 to 36°C and filtered

c) readjusting the pH of filtrate obtained from step (b) to 2.0- 3.0 preferably to 2.5 to 2.7 using acid at a temperature in the range of 10-50 °C preferably at 15 to 36°C

d) isolating Form D of cefdinir of the formula (I) from step (c)

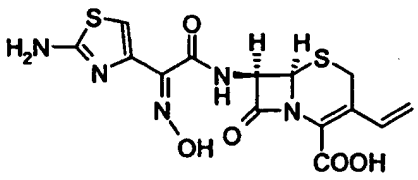
Description of Figures

Figure 1: Powder XRD pattern of crystalline Form D of cefdinir of formula (I).

Figure 2: Infrared Spectrum of crystalline Form D of cefdinir of formula (I).

Detailed description of the invention

The present invention provides novel crystalline Form D of cefdinir of the formula (I)



(I)

having substantially the same X-ray diffractogram as set out in FIG. 1 and substantially the same IR spectrum, in a KBr, as set out in FIG. 2.

In an embodiment of the present invention, novel crystalline Form D of cefdinir of the formula (I) is characterized by X-ray powder diffraction pattern with characteristic peaks of following 2θvalues

2-Theta	*I/I_o*
5.301	**8.36**
8.399	**8.27**
10.619	**100**
11.859	**18.99**
14.101	**35.03**
15.119	**12.74**
18.6	**10.67**
18.98	**6.97**
21.32	**24.79**
22.18	**8.23**
23.701	**21.46**
23.96	**12.33**
24.6	**8.18**
25.819	**15.17**
27.54	**32.7**
28.36	**13.89**
28.6	**17.75**
29.161	**7.88**
30.519	**6.15**
32.18	**5.85**
35.94	**7.62**
38.94	**7.21**

In another embodiment of the present invention, step (i) of condensing compound of formula III with compound of formula IV in the presence of base selected from

triethylamine, N-methylpiperidine, N,N-diisopropylethylamine or trimethylamine, pyridine, morpholine, piperidine, aniline triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, N-methylmorpholine or mixtures thereof; preferably in triethylamine and solvent selected from ethanol, methanol, isopropanol, Tetrahydrofuran (THF), acetone, butan-2-one, acetonitrile, dioxane, N,N-dimethylformamide (DMF), N,N'dimethylacetamide (DMAc), water or a mixture thereof preferably mixture of water and THF

In an embodiment of the present invention, in step (ii) compound M is selected from ammonium hydroxide, dicyclohexylamine, N,N'-dibenzyl ethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene(DBU), 1,5-diazabicyclo (4.3.0)non-5-ene, N,N'-dicyclohexylethylenediamine (DDA), N,N'-diphenyl ethylenediamine,1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine and the like preferably N,N'-dicyclohexylethylenediamine (DDA)

In another embodiment of the present invention, acid selected for hydrolyzing the trityl group is selected from an inorganic acid such as hydrochloric acid, hydrobromicacid, hydroiodic acid, sulphuric acid, lewis acid such as aluminum chloride, boron trifluoride, boron trifluoride etherate and the like, an organic acid such as acetic acid, formic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulphonic acid, p-toluenesulfonic aicd, and the like preferably hydrochloric acid.

In another embodiment of the present invention, N,N'-dicyclo hexylethylenediamine (DDA) salt obtained from step (ii) is crystalline

In another embodiment of the present invention, cefdinir salt obtained step (ii) or compound of formula II is converted to Cefdinir Form D by dissolving in solvents selected from C_{1-4} alcohol, acetone, acetonitrile, THF, Dimethylformamide (DMF), Dimethylacetamide (DMAc), dimethylsulfoxide (DMSO), ethyl acetate, and water or their mixtures thereof preferably in the mixture of water and acetone

In another embodiment of the present invention, solution obtained from step (iii; (a)) pH is adjusted to 4.0 - 6.5 using alkali metal hydroxides like sodium hydroxide, potassium hydroxide, alkali metal carbonates and bicarbonates like sodium carbonate, potassium carbonate, potassium bicarbonate, sodium bicarbonate and ammonia preferably with ammonia solution and treating with charcoal at a temperature in the range of 10-50 °C preferably at 15 to 36°C and filtered.

In yet another embodiment of the present invention, the crystalline form (Crystal D) of cefdinir obtained is having moisture content 13-18%, preferably 15%.

In still another embodiment of the present invention the pH of the filtrate obtained from step (iii; (b)) is readjusted to 2.5 to 2.7 at a temperature in the range of 10-50 °C preferably at 15-36 °C.

In yet another embodiment of the present invention, the compound of formula (I) obtained is a syn isomer.

The foregoing technique has been found to be markedly attractive, both from commercial point of view, as well as from manufacturing viewpoint and affords good quality of Cefdinir Form D of the formula (I).

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure.

The present invention is provided by the examples given below, which are provided by way of illustration only and should not be considered to limit the scope of the invention.

Example 1

Preparation of N,N'-dicyclohexylethane-1,2-diamine salt of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid from 7-amino-3-vinyl-3-cephem-4-carboxylic acid (Cefdinir DDA salt)

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (100 gm) in a mixture of tetrahydrofuran (500 mL) and water (62.5 mL), triethylamine (90 gm) was added at 20±2 °C. 2-Mercaptobenzothiazolyl (Z)-(2-aminothiazol-4-yl)-2-

(trityloxyimino)acetate (260 gm) was added and was stirred at 32±2 °C for 4-6 hours. The reaction was monitored by HPLC. After completion of the reaction, the THF was distilled off to get residue. To the residue, acetone (600 mL) and aqueous Hydrochloric acid (400 mL) were added and heated to reflux and maintained for 35 minutes then chilled acetone (3600mL) was added and pH was adjusted to 2.0-2.5 with triethylamine. A solution of N,N'-dicyclohexylethane-1,2-diamine in isopropyl alcohol (80 gm in 200 mL) was added to the filtrate and stirred for 60 minutes. The product thus obtained was filtered, washed with acetone and dried to get the title compound 220 gm [HPLC purity 98.27% and water content 1.0%].

Example 2

Preparation of N,N'-dicyclohexylethane-1,2-diamine salt of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid from 7-amino-3-vinyl-3-cephem-4-carboxylic acid

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (50 gm) in a mixture of tetrahydrofuran (300 ml) and water (37.5 ml), triethylamine (45 gm) was added at 20±2 °C. 2-Mercaptobenzothiazolyl (Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino)acetate (130 gm) was added and was stirred at 32±2 °C for 4-6 hours. The reaction was monitored by HPLC. After completion of the reaction, the THF was distilled off to get residue. To the residue acetone (300 ml) and aqueous Hydrochloric acid (200 ml) were added and heated to reflux and maintained for 35 minutes then chilled acetone (1800 ml) added and pH was adjusted to 2.0-2.5 with ammonia solution. A solution of N,N'-dicyclohexylethane-1,2-diamine in a mixture acetone and methanol (40 gm in 200 ml;(1:1)) was added to the filtrate to adjust the pH of the solution to 5.5 –5.75 and stirred. The product thus obtained was filtered, washed with acetone and dried to get the title compound 135.5 gm [HPLC purity 97.11% and water content 1.66%].

Example: 3

Preparation of N,N'-dicyclohexylethane-1,2-diamine salt of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid from 7-amino-3-vinyl-3-cephem-4-carboxylic acid

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (10 gm) in a mixture of DMAc (60 ml) and water (7.5 ml), triethylamine (9.0 gm) was added at 20±2 °C. 2-mercaptobenzothiazolyl (Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino) acetate (26 gm) was added and was stirred at 32±2 °C for 4-6 hours. The reaction was monitored by HPLC. After completion of the reaction, acetone (40 ml) and aqueous Hydrochloric acid (43 ml) were added and reaction mixture was heated to reflux for 2 hours. The reaction was monitored by HPLC. Acetone (500 ml) was added and pH was adjusted to 2.5 with ammonia. A methanolic solution of N,N'-dicyclohexylethane-1,2-diamine (8 gm in 25 ml) was added to the filtrate to adjust the pH of the solution to 5.5 –5.75 and stirred for 30 minutes. The product thus obtained was filtered, washed with acetone and dried to get title compound 23.1 gm [HPLC purity 98.77% and water content 2.46%].

Example: 4

Preparation of N,N'-dicyclohexylethane-1,2-diamine salt of 7β-[2-(2-amino-4-thiazolyl)-2-(Z-hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid from 7-amino-3-vinyl-3-cephem-4-carboxylic acid

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (10 gm) in a mixture of DMF (60 ml) and water (7.5 ml), triethylamine (9.0 gm) was added at 20±2 °C. 2-mercaptobenzothiazolyl (Z)-(2-aminothiazol-4-yl)-2-(trityloxyimino) acetate (26 gm) was added and was stirred at 32±2 °C for 4-6 hours. The reaction was monitored by HPLC. After completion of the reaction, acetone (40 ml) and aqueous hydrochloric acid (43 ml) were added and reaction mixture was heated to

reflux for 2 hours. The reaction was monitored by HPLC. Acetone (500 ml) was added and pH was adjusted to 2.5 with ammonia. A methanolic solution of N, N'-dicyclohexylethane-1,2-diamine (8 gm in 25 ml) was added to the filtrate to adjust the pH of the solution to 5.5 –5.75 and stirred for 30 minutes. The product thus obtained was filtered, washed with acetone and dried to get the title compound 23.1 gm [HPLC purity 98% and water content 1.00%].

Example 5

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (125g) is stirred in a mixture of water (3750mL) and acetone (250mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (100mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C. The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and is air dried to get Cefdinir D 66.5g [HPLC assay 98-99% (OAB), water content 15.07 %,]

Example 6

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (50g) is stirred in a mixture of water (1500mL) and Methanol (100mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (55mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C.

The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and is air dried to get Cefdinir D: 26.5g [HPLC assay 99-99.5%, water content 14.49 %]

Example 7

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (50g) is stirred in a mixture of water (1500mL) and acetonitrile (100mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (55mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C. The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and is air dried to get Cefdinir D: 26.4g [HPLC assay 99-99.5%, water content 14.69 %]

Example 8

Cefdinir DDA salt (50g) is stirred in a mixture of water (1500mL) and isopropyl alcohol (100mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (55mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C. The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and dried to get Cefdinir D: 26.5g [HPLC assay 99-99.5%, water content 14.84 %]

Example 9

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (50g) is stirred in a mixture of water (1500mL) and dimethylformamide (100mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (55mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C. The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and is air dried to get Cefdinir D: 27.08g [HPLC assay 99-99.5%, water content 14.75 %]

Example 10

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (25g) is stirred in a mixture of water (750mL) and dimethylsulfoxide (50mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (27.5mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C. The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and is air dried to get Cefdinir D: 13.2g [HPLC assay 99-99.5%, water content 14.52 %]

Example 11

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (25g) is stirred in a mixture of water (750mL) and Ethylacetate (50mL) at 35 to 38°C. Aqueous Hydrochloric acid is added to adjust pH to 1.2-1.8. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using ammonia solution (27.5mL). Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using aqueous Hydrochloric acid to get a clear solution. Then pH is readjusted to 2.5 using ammonia solution at 10 to 15°C. The white slurry is stirred for 3 hours. Then the precipitate is filtered, washed with water and is air dried to get Cefdinir D: 13.2g [HPLC assay 99-99.5%, water content 14.52 %]

Example 12

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (10 g) is stirred in a mixture of solvent of water (150mL) and acetone (20mL) at 35 to 38°C. Hydrochloric acid is added to adjust pH to 1.5. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using sodium hydroxide solution. Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using hydrochloric acid. Then pH is readjusted to 2.5 using sodium hydroxide solution at 10 to 15°C. After precipitation of the product, the white slurry is stirred for 3 hours at 5 to 10°C. Then the precipitate is filtered and is air dried to get Cefdinir D 5.2 g. [HPLC assay 99-99.4%, water content 14.39 %]

Example 13

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (25 g) is stirred in a mixture of solvent of water (750mL) and acetone (50mL) at 35 to 38°C. Hydrochloric acid is added to adjust pH to 1.5. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using sodium bicarbonate solution. Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using hydrochloric acid. Then pH is readjusted to 2.5 using sodium hydroxide solution at 10 to 15°C. After precipitation of the product, the white slurry is stirred for 3 hours at 5 to 10°C. Then the precipitate is filtered and is air dried to get Cefdinir D 13.6 g. [HPLC assay 99-99.5%, water content 14.28 %]

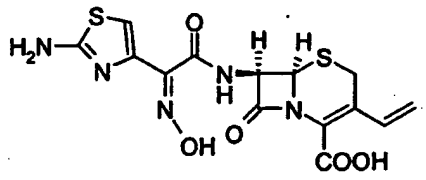
Example 14

Preparation of 7-[[(2-aminothiazol-4-yl)-(z)(hydroxyimino)] acetyl] amino-3-vinyl-3-cephem-4-carboxylic acid (Form D) from Cefdinir DDA salt:

Cefdinir DDA salt (25 g) is stirred in a mixture of solvent of water (750mL) and acetone (50mL) at 35 to 38°C. Hydrochloric acid is added to adjust pH to 1.5. After stirring for 5 to 10 minutes, pH is adjusted to 6.0 using potassium carbonate solution. Then carbon is added and stirred at 35 to 38°C for 30 minutes. The filtrate is cooled to 15°C and pH is adjusted to 1.5 using hydrochloric acid. Then pH is readjusted to 2.5 using sodium hydroxide solution at 10 to 15°C. After precipitation of the product, the white slurry is stirred for 3 hours at 5 to 10°C. Then the precipitate is filtered and is air dried to get Cefdinir D 13.4 g. [HPLC assay 99-99.5%, water content 14.23 %]

We claim:

1. Novel crystalline Form D of cefdinir of the formula (I)



(I)

having substantially the same X-ray diffractogram as set out in FIG. 1 and substantially the same IR spectrum, in a KBr, as set out in FIG. 2.

2. The Crystalline Cefdinir Form D of claim 1, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks of following 2θ values:

2-Theta	*I/I_o*
5.301	8.36
8.399	8.27
10.619	100
11.859	18.99
14.101	35.03
15.119	12.74
18.6	10.67
18.98	6.97
21.32	24.79
22.18	8.23
23.701	21.46
23.96	12.33
24.6	8.18
25.819	15.17
27.54	32.7
28.36	13.89
28.6	17.75
29.161	7.88
30.519	6.15
32.18	5.85
35.94	7.62
38.94	7.21

3. Crystalline substance of claim 1, which is characterized by infrared absorption spectrum pattern having characteristic peaks at approximately 3301.4, 2980.9, 2898.4, 1786.1, 1760.2, 1667.4, 1610.1, 1544.4, 1458.2, 1429.3, 1419.5, 1349.3, 1334.4, 1299.1, 1285.9, 1191.2, 1136.0, 1121.8, 1064.2, 1049.7, 1016.1, and 993.1 Cm^{-1}

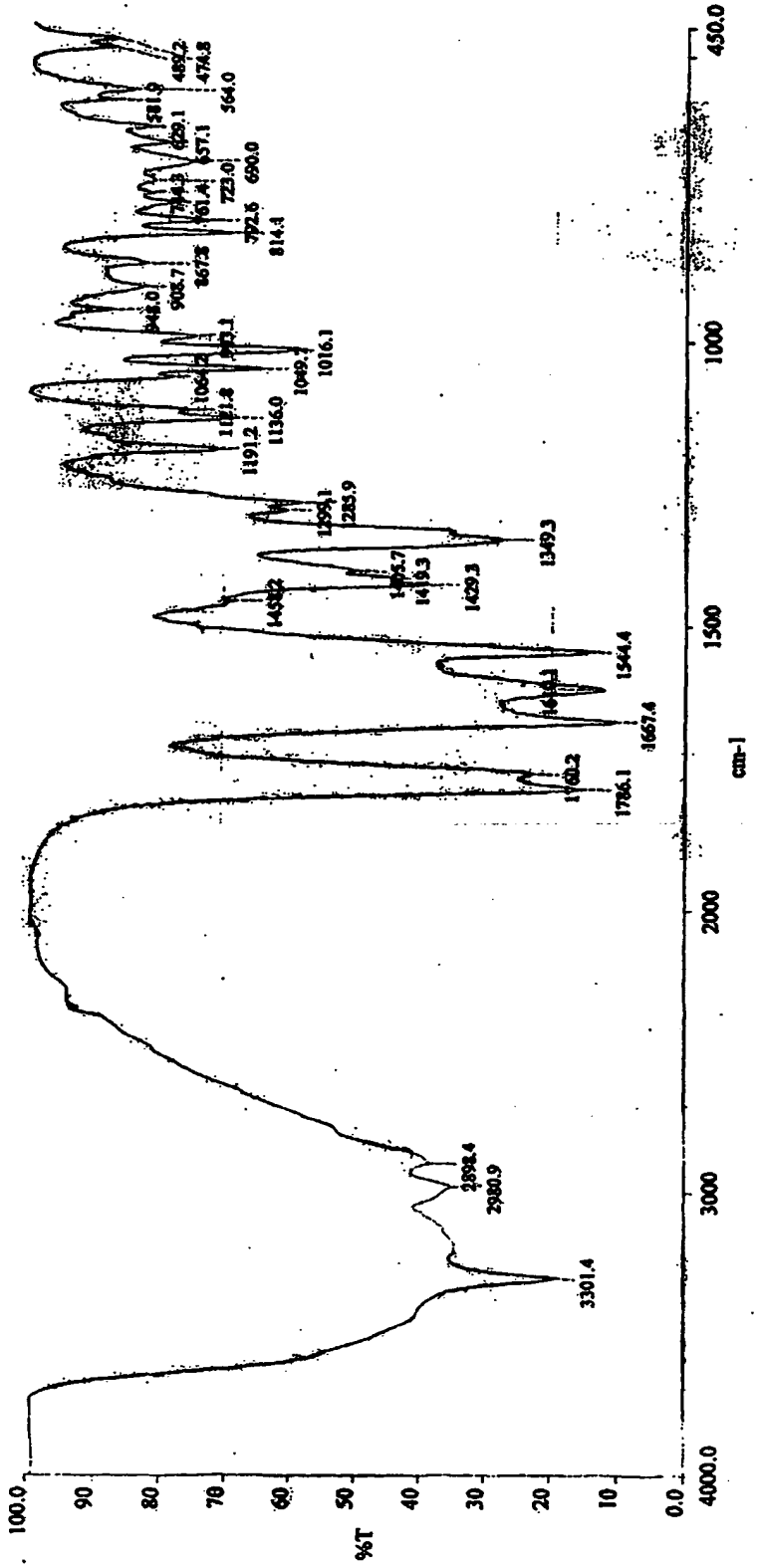

100.0
90
80
70
60
50
40
30
20
10
0.0
%T
4000.0
3000
2000
1500
1000
450.0
cm-1
3301.4
2980.9
1667.4
1544.4
1429.3
1349.3
1136.0
1049.7
1016.1
814.4
690.0
564.0
474.8

FIGURE : 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 2005/000652

A. CLASSIFICATION OF SUBJECT MATTER
IPC[7]: C07D 501/22
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[7]: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI, PAJ, EPODOC, REGISTRY, CEPLUS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/104010 A1 (RANBAXY LABORATORIES LIMITED) 2 December 2004 (02.12.2004) *the whole document, esp. pages 3 and 4, examples, figures, claims.*	2,3
P,X	US 2004/0242556 A1 (R. DANDALA et al.) 2 December 2004 (02.12.2004) *the whole document, esp. fig. 3.*	3
X	US 6350869 B1 (H. STURM et al.) 26 February 2002 (26.02.2002) *the whole document, esp. column 2, example 2, claims.*	2,3

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 June 2005 (08.06.2005)	24 June 2005 (24.06.2005)
Name and mailing address of the ISA/ AT **Austrian Patent Office** Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24 / 535	Authorized officer WENIGER S. Telephone No. +43 / 1 / 534 24 / 341

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 2005/000652

Continuation of first sheet

Certain claims were found unsearchable:

Observations where certain claims were found unsearchable
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 1 because they relate to subject matter not required to be searched by this Authority, namely:

Claim 1 does not comprise any inventive technical feature, but references to parts of the description (figures), only.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB 2005/000652

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
US	A	20040242556				none	
US	B1	6350869	2002-02-26	CN	A	1251590	2000-04-26
				NO	A	994466	1999-09-15
				TR	T2	9902406T	2000-02-21
				SK	A3	134399	2000-05-16
				PL	A1	335620	2000-05-08
WO	A1	2004104010	2004-12-02			none	